CLAIMS

1. A method of producing a multimeric member of a specific binding pair (sbp), which method comprises:
expressing in a recombinant host organism a first polypeptide chain of said sbp member or a genetically diverse population of that type of sbp member fused to a component of a secreted replicable genetic display package (rgdp) which thereby displays polypeptide at the surface of the package, and expressing in a recombinant host organism a second polypeptide chain of said multimer and causing or allowing the polypeptide chains to come together to form said multimer as part of said rgdp, at least one of said polypeptide chains being expressed from nucleic acid that is capable of being packaged using said component therefor, whereby the genetic material of each said rgdp encodes a said polypeptide chain.

2. A method according to claim 1 wherein both said chains are expressed in the same host organism.

3. A method according to claim 2 wherein said first and second chains of said multimer are expressed as separate chains from a single vector containing their respective nucleic acid.

4. A method according to any one of claims 1, 2 and 3 wherein at least one of said polypeptide chains is expressed from a phage vector.

5. A method according to any one of claims 1 to 4 wherein at least one of said polypeptide chains is expressed from a phagemid vector, the method including using a helper phage, or a plasmid expressing complementing phage genes, to help package said phagemid genome, and said component of the rgdp is a capsid protein therefor.

6. A method according to claim 5 wherein said capsid protein is absent, defective or conditionally defective in the helper phage.

7. A method according to any one of the preceding claims which comprises introducing a vector capable of expressing said first polypeptide chain into a host organism which expresses said second polypeptide chain in free form, or introducing a vector capable of expressing said second polypeptide in free form into a host organism which expresses said first polypeptide chain.

8. A method according to any one of the preceding claims wherein each said polypeptide chain is expressed from nucleic acid which is capable of being packaged as a rgdp using said component fusion product, whereby encoding nucleic acid for both said polypeptide chains are packaged in respective rgdps.

9. A method according to any one of the preceding claims wherein the nucleic acid encoding at least one of said first and second polypeptide chains is obtained from a library of nucleic acid including nucleic acid encoding said chain or a population of variants of said chain.

10. A method according to claim 9 wherein both the first and second polypeptide chains are obtained from respective said libraries of nucleic acid.

11. A method of producing a member of a specific binding pair (sbp) from a nucleic acid library including nucleic acid encoding said sbp member or a genetically diverse population of that type of sbp member, which method comprises: expressing in recombinant host cells polypeptides encoded by said library nucleic acid fused to a component of a secreted replicable genetic display package (rgdp) or in free form for association with a polypeptide component of said sbp member which is expressed as a fusion to said rgdp component, so that the rgdp displays

said sbp member in functional form at the surface of the package, said library nucleic acid being contained within the host cells in a form that is capable of being packaged using said rgdp component, whereby the genetic material of an rgdp displaying an sbp member contains nucleic acid encoding said sbp member or a polypeptide component thereof.

12. A method of producing a member of a specific binding pair (sbp), which method comprises:

expressing in recombinant host cells nucleic acid encoding said sbp member or a genetically diverse population of that type of sbp member, wherein the or each sbp member or a polypeptide component thereof is expressed as a fusion with a component of a secreted replicable genetic display package (rgdp) which displays said sbp member at the surface of the package, nucleic acid encoding said sbp member or a polypeptide component thereof being contained within the host cell in a form that is capable of being packaged using said rgdp component, whereby the genetic material of the rgdp displaying said sbp member encodes said sbp member or a polypeptide component thereof, said host organism being a mutator strain which introduces genetic diversity into the sbp member to produce said mixed population.

13. A method of producing a member of a specific binding pair (sbp), which method comprises:

expressing in recombinant host cells nucleic acid encoding said sbp member or a genetically diverse population of that type of sbp member, wherein the or each said sbp member or a polypeptide component thereof is expressed as a fusion with a component of a secreted replicable genetic display package (rgdp) which displays said sbp member in functional form at the surface of the package, nucleic acid encoding said sbp member or a polypeptide component thereof being contained within the host cell in a form that is capable of being packaged using said rgdp

component, whereby the genetic material of the rgdp displaying an sbp member encodes said sbp member or a polypeptide component thereof, said fusions being with bacteriophage capsid protein and the rgdps being formed with said fusions in the absence of said capsid protein expressed in wild-type form.

14. A method of producing a member of a specific binding pair (sbp) which method comprises:

expressing in recombinant host cells nucleic acid encoding said sbp member or a genetically diverse population of that type of sbp member, wherein the or each sbp member or a polypeptide component thereof is expressed as a fusion with a component of a secreted replicable genetic display package (rgdp) which displays said sbp member at the surface of the package, nucleic acid encoding said sbp member or a polypeptide component thereof being contained within the host cell in a form that is capable of being packaged using said rgdp component, whereby the genetic material of the rgdp displaying an sbp member encodes said sbp member or a polypeptide component thereof, said sbp member or polypeptide component thereof being expressed from a phagemid as a capsid fusion, and a helper phage, or a plasmid expressing complementing phage genes, is used along with said capsid fusions to package the phagemid nucleic acid.

15. A method according to claim 14, wherein said capsid protein is absent, defective or conditionally defective in the helper phage.

16. A method according to any one of claim 13 to 15 wherein the host cell is a mutator strain which introduces genetic diversity into the sbp member nucleic acid.

17. A method according to any one of claims 9 to 16 wherein said library or genetically diverse population is obtained from:

(i) the repertoire of rearranged immunoglobulin genes of an animal immunised with complementary sbp member,

(ii) the repertoire of rearranged immunoglobulin genes of an animal not immunised with complementary sbp member,

(iii) a repertoire of an artificially rearranged immunoglobulin gene or genes,

(iv) a repertoire of an immunoglobulin homolog gene or genes, or

(v) a mixture of any of (i), (ii), (iii) and (iv).

18. A method according to any one of the preceding claims wherein said sbp member comprises a domain which is, or is homologous to, an immunoglobulin domain.

19. A method according to any one of the preceding claims wherein the rgdp is a bacteriophage, the host is a bacterium, and said component of the rgdp is a capsid protein for the bacteriophage.

20. A method according to claim 19 wherein the phage is a filamentous phage.

21. A method according to claim 20 wherein the phage is selected from the class I phages fd, M13, f1, If1, 1ke, ZJ/Z, Ff and the class II phages Xf, Pf1 and Pf3.

22. A method according to claim 20 or claim 21 wherein said sbp member or polypeptide chain thereof is expressed as a fusion with the gene III capsid protein of phage fd or its counterpart in another filamentous phage.

23. A method according to claim 22 wherein said sbp member or polypeptide chain thereof is inserted in the N-terminal region of the mature capsid protein downstream of a secretory leader peptide.

24. A method according to any one of claims 19 to 23 wherein the host is E.coli.

25. A method according to any one of the preceding claims wherein nucleic acid encoding an sbp member polypeptide is linked downstream to a viral capsid protein through a suppressible translational stop codon.

26. A method according to any one of the preceding claims wherein the rgdps formed by said expression are selected or screened to provide an individual sbp member or a mixed population of said sbp members associated in their respective rgdps with nucleic acid encoding said sbp member or a polypeptide chain thereof.

27. A method according to claim 26 wherein the rgdps are selected by affinity with a member complementary to said sbp member.

28. A method according to claim 27 which comprises recovering any rgdps bound to said second member by washing with an eluant.

29. A method according to claim 28 wherein the eluant contains a molecule which competes with said rgdp for binding to the complementary sbp member.

30. A method according to any one of the claims 27 to 29 wherein the rgdp is applied to said complementary sbp member in the presence of a molecule which competes with said package for binding to said complementary sbp member.

31. A method according to any one of claims 26 to 30, wherein nucleic acid derived from a selected or screened rgdp is used to express said sbp member or a fragment or derivative thereof in a recombinant host organism.

32. A method according to claim 31 wherein nucleic acid from one or more rgdps is taken and used to provide encoding nucleic acid in a further said method to obtain an individual sbp member or a mixed population of sbp members, or encoding nucleic acid therefor.

33. A method according to claim 31 or claim 32 wherein the expression end product is modified to produce a derivative thereof.

34. A method according to any one of claim 31, 32 and 33 wherein the expression end product or derivative thereof is used to prepare a therapeutic or prophylactic medicament or a diagnostic product.

35. Recombinant host cells harbouring a library of nucleic acid fragments comprising fragments encoding a genetically diverse population of a type of member of a specific binding pair (sbp), each sbp member or a polypeptide component thereof being expressed as a fusion with a component of a secretable replicable genetic display package (rgdp), so that said sbp members are displayed on surface of the rgdps in functional form and the genetic material of the rgdps encode the associated sbp member or a polypeptide component thereof.

36. Recombinant host cells according to claim 35, wherein said type of sbp member are immunoglobulins or immunoglobulin homologs, a first polypeptide chain of which is expressed as a said fusion with a component of the rgdp and a second polypeptide chain of which is expressed in free form and associates with the fused first polypeptide chain in the rgdp.

37. A helper phage whose genome lacks nucleic acid encoding one of its capsid proteins, or whose encoding nucleic acid therefor is conditionally defective, or which encodes said capsid protein in defective or conditionally defective form.

38. A bacterial host cell containing a filamentous phage genome defective for a capsid protein thereof and wherein the host cell is capable of expressing capsid protein complementing said defect such that infectious phage particles can be obtained therefrom.

39. A bacterial host cell according to claim 38 wherein said complementing capsid protein is expressed in said host from another vector contained therein.

40. A bacterial host cell according to claim 38 or claim 39 wherein the defective capsid protein is gene III of phage fd or its counterpart in another filamentous phage.

41. Recombinant E.coli TG1 M13K07 gIII No. 3 (NCTC 12478).

42. A phage having the form of a replicable genetic display package displaying on its surface in functional form a member of a specific binding pair or a binding domain thereof.

43. A kit for use in carrying out a method according to any one of claims 1 to 34, said kit including:

(i) at least one vector having an origin of replication for single-stranded bacteriophage, a restriction site for insertion of nucleic acid encoding said sbp member or a polypeptide component thereof in the 5' end region of the mature coding sequence of a phage capsid protein, and with a secretory leader sequence upstream of said site which directs a

fusion f the capsid protein and sbp polypeptide to the periplasmic space of a bacterial host; and

(ii) ancillary components required for carrying out the method.